Cytokine 88 (2016) 51–56

Contents lists available at ScienceDirect

Cytokine

journal homepage: www.journals.elsevier.com/cytokine

Comparison of peri-implant clinical and radiographic inflammatory parameters and whole salivary destructive inflammatory cytokine profile among obese and non-obese men

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ARTICLE INFO

Article history:
Received 17 June 2016
Received in revised form 13 August 2016
Accepted 18 August 2016

Keywords:
Bleeding on probing
Dental implant
Obesity
Inflammation
Cytokine
Bone loss

ABSTRACT

The aim of the present cross-sectional retrospective study was to compare the peri-implant clinical and radiographic inflammatory parameters and whole salivary destructive inflammatory cytokine profile among obese and non-obese men. Thirty-five obese and 37 non-obese men were included. Information regarding age, obesity, systemic health status, and habits was collected using a questionnaire. Clinical examination to evaluate peri-implant parameters and radiographic examination to assess marginal bone loss were conducted. Levels of interleukin (IL)-6 and IL-1β in collected un-stimulated whole saliva were measured using enzyme-linked immunosorbent assay. Data was statistically analyzed using Kruskal Wallis test. The mean scores of peri-implant bleeding on probing ($P < 0.05$) and peri-implant probing depth ($P < 0.05$) were significantly higher among obese compared with non-obese individuals. The mean marginal bone loss was also statistically significantly higher among individuals in the test-group compared with the control-group ($P < 0.05$). Whole salivary IL-1β ($P < 0.001$) and IL-6 ($P < 0.001$) levels were significantly higher among individuals in the test-group compared with the control-group. Clinical and radiographic peri-implant inflammatory parameters were worse, and whole salivary IL-6 and IL-1β were higher in obese than non-obese subjects. Obese patients are at greater risk of peri-implant inflammation than non-obese healthy subjects. It is highly recommended that clinicians should educate obese patients seeking implant treatment regarding the association between obesity and peri-implant inflammation. In addition, obese patients with osseointegrated implants must follow strict oral hygiene regimen to prevent inflammation and maintain optimum peri-implant tissue health.

1. Introduction

Peri-implant diseases (peri-implant mucositis and peri-implantitis) and periodontitis are inflammatory conditions that jeopardize the soft tissues and alveolar bone around implants and teeth, respectively [1,2]. If left untreated, these inflammatory conditions may lead to suppuration, loss of supporting alveolar bone and ultimately implant failure and tooth loss, correspondingly [1]. Besides local risk-factors such as poor oral hygiene status, tobacco smoking and previous history of periodontitis [3,4]; systemic conditions that have been associated with the etiology of periimplant diseases and periodontitis include poorly-controlled diabetes mellitus, acquired immune deficiency syndrome and osteoporosis [5–7]. Obesity (accumulation of superfluous amounts of fat in the body, to a degree that may debilitate health [8,9]) is also a significant risk-factor of periodontitis. According to World Health Organization criteria [8], individuals with body mass index (BMI) over 30 kg/m^2 are categorized as "obese". Around 300 million individuals are estimated to be obese globally [10]. According to Atabay et al. [11], obesity may enhance periodontal destruction by elevating oxidative stress in periodontal tissues. *In-vitro* results by Huang et al. [12] demonstrated that obesity compromises the efficiency of the innate periodontal immune response by decreasing infiltration and activation of macrophages thereby further aggravating periodontal inflammation. However, it is pertinent to mention that there are no studies in indexed literature that have

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http://dx.doi.org/10.1016/j.cyto.2016.08.017
1043-4666/

assessed the influence of obesity on peri-implant soft and hard tissue status.

Unstimulated whole saliva is a complex oral fluid that can be collected non-invasively. Under oral inflammatory conditions, such as periodontitis and peri-implant diseases, unstimulated whole saliva expresses raised levels of destructive inflammatory cytokines which makes unstimulated whole saliva a useful investigative tool for the evaluation of oral inflammatory conditions [13–17]. However, there are no studies that have compared the destructive inflammatory cytokine profile in unstimulated whole saliva of obese and non-obese individuals (controls). Since obesity is a significant risk factor for periodontitis, it is hypothesized that (a) peri-implant soft tissue inflammation and marginal bone loss are significantly higher among obese compared with non-obese individuals; and (b) levels of destructive inflammatory cytokines (interleukin [IL]-6 and IL-1beta) are significantly higher in the unstimulated whole saliva of obese compared with controls.

The aim of the present cross-sectional retrospective study was to compare the peri-implant clinical and radiographic inflammatory parameters and whole salivary destructive inflammatory cytokine profile among obese and non-obese individuals.

2. Materials and methods

2.1. Ethical guidelines

The College of Dentistry Research Centre (CDRC), King Saud University, approved the study protocol for this study. All volunteering individuals were requested to sign a consent form and were informed that reserved the right to retired from the research project at any stage of the investigation.

2.2. Study design

The present study had a cross-sectional retrospective design in which, data was gathered from a defined cohort (obese and non-obese individuals) with functioning dental implants.

2.3. Eligibility criteria

The inclusion criteria were as follows: (a) patients with obesity (patients with BMI of $\geqslant$30 kg/m^2 (test-group) [8]); (b) non-obese individuals (patients with BMI ranging from 18.5 to 24.9 kg/m^2) (control-group); and (c) patients with dental implants in function since at least 12 months. The exclusion criteria were as follows: (a) individuals that self-reported systemic diseases other than obesity (for example acquired immune deficiency syndrome, cardiovascular disorders, diabetes mellitus, hepatitis, and renal disorders); (b) lactation and pregnancy; (c) used of antibiotics, steroids and/or non-steroidal anti-inflammatory drugs within the past 3 months; (d) tobacco smoking, smokeless tobacco use and habitual alcohol consumption; (e) patients on bisphosphonates therapy; and (f) patients that received non-surgical periodontal therapy (scaling and root planning) within the past 3 months.

2.4. Participants

Obese and non-obese individuals having restored and functional implant treatment, which has been in service for at least 12 months were included. Obesity was defined as body mass index (BMI) of $\geqslant$30 kg/m^2 [8]. Individuals with BMI ranging from 18.5 to 24.9 kg/m^2 were defined as controls. All patients were assessed at the dental clinics at the College of Dentistry, King Saud University, Riyadh, Saudi Arabia.

2.5. Questionnaire

Data regarding age, gender, duration of obesity, family history of obesity, daily oral hygiene maintenance, last visit to an oral healthcare provider and implant therapy jaw location, functional duration, number of implants placed, and loading protocol (immediate or delayed loading), were collected using a questionnaire.

2.6. Collection unstimulated whole saliva samples

All unstimulated whole saliva samples were collected at early morning hours (between 7:00 and 9:00 am) by a trained and calibrated investigator (FV). The overall score for the intra-examiner reliability was 0.88. Briefly, the participants were comfortably seated on a dental chair and were requested to allow saliva to accumulate in the mouth for 5 continuous minutes. At the end of this time duration the participants were requested to expectorate into a gauged measuring cylinder. During the process saliva accumulation in the mouth the participants were advised to avoid swallowing and moving their tongue and lips. Unstimulated whole salivary flow rate was determined by dividing the total amount of saliva collected in the measuring cylinder by 5. Unstimulated whole salivary flow rate was expressed in milliliters per minute (ml/min) [18–20]. All salivary samples were assessed within 3 months of collection.

2.7. Assessment of destructive inflammatory cytokine (IL-6 & IL-1β) levels in unstimulated whole saliva

Levels of IL-6 and IL-1β in unstimulated whole saliva samples were investigated using enzyme-linked immunosorbent assay (ELISA). All laboratory based investigations were performed by a trained and calibrated examiner (MAK). The kappa score for intra-examiner reliability was 0.88. In summary, unstimulated whole saliva samples were diluted (1:100) in phosphate-buffered saline and the 96-well plates were coated in duplicate with specific protein antibodies. The 96-well plates were kept at room temperature for 60 min and then washed 3 times. A conjugate solution was added to the plates, following which they were re-incubated for 120 min. Fifty ml of stop solution was added to terminate color formation. The sensitivity of ELISA was 99% and 98.6% for whole salivary IL-6 and IL-1β levels, respectively.

2.8. Evaluation of clinical and radiographic parameters peri-implant inflammation

Clinical examinations were carried out by one trained and calibrated investigator (TA). The overall *kappa* for intra-examiner reliability was 0.92. Among obese individuals and controls, peri-implant bleeding on probing [21] and peri-implant probing depth [22] were measured at six sites per implant (mesiobuccal, midbuccal, distobuccal, distolingual/palatal, midlingual/palatal and mesiolingual/palatal). Peri-implant probing depth was measured to the nearest millimeter using a graded periodontal probe (Hu-Friedy, Chicago, IL, USA) [23].

Intra-oral digital bitewing radiographs were taken for each implant by a trained and calibrated examiner (FAS). The overall *kappa* for the intra-examiner reliability was 0.88. The radiographic technique was standardized by using a film holder as a guiding tool for X-ray beams (Belmont ACURAY 071A Intra Oral X-ray System, Hudson, FL, USA). Marginal bone loss was defined as the linear distance from the implant-abutment junction to the most coronal part of the alveolar crest [24]. Marginal bone loss was recorded in millimeters using a software program (Scion Image, Scion Corp., Fredrick, Maryland, USA).

2.9. Statistical analysis

Statistical analysis was performed using a software (SPSS v.18, IBM, Chicago, IL). Overall characteristics of the study cohort were analyzed using descriptive statistics (mean, standard deviation, frequencies & percentages). Clinical (peri-implant bleeding on probing and peri-implant probing depth) and radiographic (marginal bone loss) inflammatory parameters and whole salivary cytokine levels among obese and non-obese participants were assessed and compared using the Kruskal Wallis test. Power analysis was performed with a computer software (nQuery Advisor 5.0 (Statistical Solutions, Saugus, Massachusetts, USA). Power analysis was based on the supposition that a mean difference of 0.5 mm and 1 mm in peri-implant marginal bone loss and peri-implant probing depth, respectively should be detected between obese patients and controls at a significance level of 0.05 and a desired study power of at least 80%. It was estimated that a sample size of 35 individuals per group will achieve 90% power with a 0.05 two-sided significance level. P-values less than 0.05 were considered statistically significant.

3. Results

3.1. General characteristics of the study population

Thirty-five were included in the test-group and 37 individuals were included in the control-group. All participants were male. The mean ages of individuals in the test and control groups were 44.05 years (35.4–54.7) and 43.1 years (33.7–52.5 years), respectively. The mean BMI of individuals in the test-group (35.2 kg/m^2 [33.6–38.2 kg/m^2]) was statistically significantly higher than the control group (24.3 kg/m^2 [22.5–27.3 kg/m^2]) ($P < 0.05$). The mean duration of obesity in the test-group was 6.5 years (5.3–7.2 years). A family history of obesity was more often reported by individuals in the test-group (77.1%) compared with the control-group (8.1%) (Table 1).

Table 1
General characteristics of the study population.

Parameters	Obese individuals	Control individuals
Number of participants	35	37
Gender (male)	35	37
Mean age (range) in years	44.05 (35.4–54.7)	43.1 (33.7–52.5)
Body mass index (kg/m^2)	36.2 (33.6–38.2)[a]	24.3 (22.5–27.3)
Duration of obesity in years	6.5 (5.3–7.2)	–
Family history of obesity (%)	77.1%	8.1%
Total number of implants	45	48
Number of implants placed in the maxilla	4	6
Number of implants placed in the mandible[b]	41	42
Time of implant loading (in months)	3.3 (3–4)	3.5 (3–4.2)
Duration of implants in function (in years)	6.8 (2–8)	6.2 (4–10)
Daily oral tooth brushing		
Once daily	91.4	89.1
Twice daily	8.6	10.9
Last visit to an oral healthcare provider		
Within 6 months (%)	–	–
Over 1 year (%)	–	–
Over 2 years (%)	–	–
Over 3 years (%)	100%	100%

[a] Compared with controls ($P < 0.05$).
[b] All implants were placed in the regions of missing premolar and/or molar teeth.

3.2. Implant related characteristics of the study population

The total number of dental implants (ITI-Straumann AG, Peter Merian-Weg, Basel, Switzerland) placed in the test and control groups were 45 and 48 implants, respectively most of which, were placed in the mandible. Among patients in the test and control groups, implants had been in function since a mean duration of 6.5 years (2–8 years) and 6.2 years (4–10 years), respectively. In both groups, delayed loaded dental implants were used. All implants were placed in the regions of missing premolar and/or molar teeth (Table 1). In both groups, dental implants with moderately rough surfaces were used with lengths and diameters ranging between 3.8–4.1 mm and 11–13 mm, respectively. In both groups, cement-retained prosthesis were used.

3.3. Daily oral hygiene maintenance

In the test and control groups, 91.4% and 89.1% individuals reported to brush their teeth once daily (Table 1). Dental flossing was reported by none of the participants in the test and control groups. None of the individuals in either group reported to have visited an oral healthcare provider within the past 36 months.

3.4. Clinical and radiographic peri-implant inflammatory parameters

The mean scores of peri-implant bleeding on probing ($P < 0.05$) and peri-implant probing depth ($P < 0.05$) were significantly higher among individuals in the test-group compared with the control-group. The mean peri-implant marginal bone loss was also statistically significantly higher among individuals in the test-group compared with the control-group ($P < 0.05$) (Table 2). There was no statistically significant difference in peri-implant bleeding on probing, peri-implant probing depth and marginal bone loss around implants in the test and control groups with reference to jaw location (data not shown).

3.5. Levels of interleukin-1 beta and interleukin-6 in unstimulated whole saliva

Whole salivary IL-1β ($P < 0.001$) and IL-6 ($P < 0.001$) levels were significantly higher among individuals in the test-group compared with the control-group (Table 3). There was no statistically significant difference in the unstimulated whole salivary flow rate among obese (0.52 ± 0.2 ml/min) and control individuals (0.55 ± 0.2 ml/min). There was no statistically significant difference in whole salivary IL-1β and IL-6 in the test and control groups with reference to jaw location (data not shown). Figs. 1 and 2 show the individual IL-1β and IL-6 levels, respectively among obese and non-obese individuals.

Table 2
Peri-implant clinical and radiographic parameters among obese and non-obese individuals.

	Obese individuals	Control individuals
Number of patients	35	37
Mean peri-implant bleeding on probing (%) (range)	28.2 (16.5–33.4)[a]	10.1 (4.5–15.1)
Mean peri-implant probing depth (%) (range)	4.4 (2.1–5.3)[a]	2.1 (1.8–2.5)
Mean peri-implant marginal bone loss (mm) (range)	3.4 (2.5–4.7)[a]	0.8 (0–2.4)

[a] Compared with controls ($P < 0.05$).

Table 3
Comparison of whole salivary interleukin-1 beta and interleukin-6 levels among obese and non-obese individuals.

Cytokines	Obese individuals	Control individuals
Number of patients	35	37
Mean IL-1β in pg/ml (range)	2462.7 (1947.5–2964.4)[a]	1088.3 (845.6–1258.4)
Mean IL-6 in pg/ml (range)	361.3 (300.5–406.2)[a]	133.2 (108.6–144.6)

[a] Compared with individuals in the control group ($P < 0.001$).

4. Discussion

To our knowledge from indexed literature, this is the first study that compared clinical, radiographic and immunologic parameters of peri-implant inflammatory parameters among patients with and without obesity. In the present study, it was hypothesized that (a) peri-implant soft tissue inflammation and marginal bone loss are significantly higher among obese compared with non-obese individuals; and (b) levels of destructive inflammatory cytokines (interleukin [IL]-6 and IL-1beta) are significantly higher in the unstimulated whole saliva of obese compared with controls. The present results support this hypothesis since peri-implant bleeding on probing, peri-implant probing depth, peri-implant marginal bone loss and levels of whole salivary IL-6 and IL-1β were statistically significantly higher among obese (test-group) compared with non-obese (control-group) patients. Although the exact explanation for these results is yet to be determined, a clarification in this regard could be postulated from the results by Atabay et al. [11] and Huang et al. [12]. According to Atabay et al. [11], obesity may enhance periodontal destruction by elevating oxidative stress in periodontal tissues. *In-vitro* results by Huang et al. [12] demonstrated that obesity compromises the efficiency of the innate periodontal immune response by decreasing infiltration and activation of macrophages thereby further aggravating periodontal inflammation. It is hypothesized that these obesity raises oxidative stress around peri-implant soft and hard tissues and also impairs the function of macrophages. However, further studies to justify this hypothesis.

Another important finding of the present study was the significantly higher levels of whole salivary IL-6 and IL-1β among obese patients as compared to controls. Both IL-6 and IL-1β are pro-inflammatory cytokines, reported to be increased in inflammatory state, and are identified as indicators of inflammatory state systemically in serum, gingival crevicular fluid and saliva for systemic and oral inflammation [25]. According to Elangovan et al. [26] there is a positive correlation between waist circumference and IL-1β levels in peri-implant sulcular fluid. Authors of the present study support the results by Elangovan et al. [26] although IL-6 and IL-1β were assessed in unstimulated whole saliva in the present study and not in peri-implant sulcular fluid. It is pertinent to mention that there is a cascade of events associated with an inflammatory reaction. According to Sims et al. [27] IL-6 and IL-11 regulate bone turnover by stimulating osteoclastogenesis and new bone formation. Likewise, raised levels of anti-inflammatory cytokines (such as IL-10) have been reported in the gingival crevicular fluid of patients and animals with periodontal disease [28,29]. These cytokines have been reported to compensate for the destructive effect of pro-inflammatory cytokines (such as IL-6 and IL-β) by reducing the severity of the inflammatory process [28,29]. It is therefore hypothesized that with high levels of IL-6 and IL-β in unstimulated whole saliva, levels of anti-inflammatory cytokines were also high in obese patients. However, the severity of chronic periodontitis on these patients may have disrupted the balance between the pro and anti-inflammatory cytokines. Further studies are needed to test this hypothesis.

A major limitation of the present study is that direct correlations between peri-implant inflammation, alveolar bone loss and whole salivary cytokine profile could not be established on an individual level in both groups (data not shown). One explanation in this regard is that none of the participants in the control group had periodontitis, and all obese patients included in the present study had a history of periodontal disease (data not shown). These factors may have influenced the peri-implant soft and hard tissue profile, as well as whole salivary cytokine levels in both groups. Therefore, further well-studies with clearly defined groups (such as: [a] obese patients with periodontitis, [b] obese patients without periodontitis, [c] non-obese patients with periodontitis, and [d] non-obese patients without periodontitis) are needed to determine whether or not the whole salivary cytokines level are influenced by obesity.

It is well known that mechanical debridement is most commonly used to eradicate plaque from teeth and implant surfaces [30–32]. In the study by Papageorgiou et al. [33] there was not statistically significant difference in clinical periodontal parameters among obese and non-obese patients following non-surgical mechanical debridement. However, recent studies have shown that adjunctive therapies such as photodynamic therapy when performed in combination with non-surgical mechanical debridement is more effective in reducing peri-implant inflammation as compared to non-surgical mechanical debridement alone [30,31] should mechanical debridement with adjunct photodynamic ther-

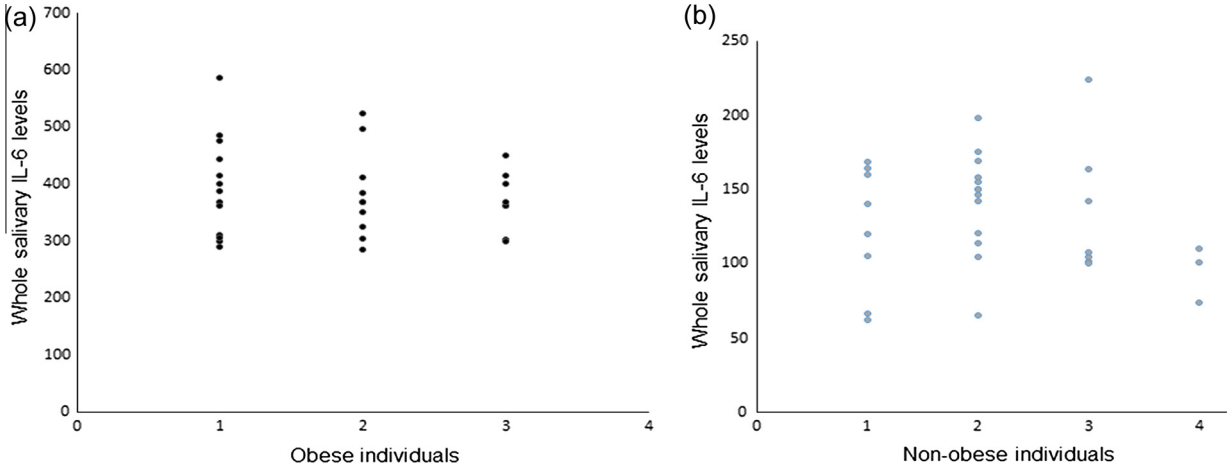

Fig. 1. Dot-plot demonstrating individual levels of IL-1β among obese and non-obese individuals.

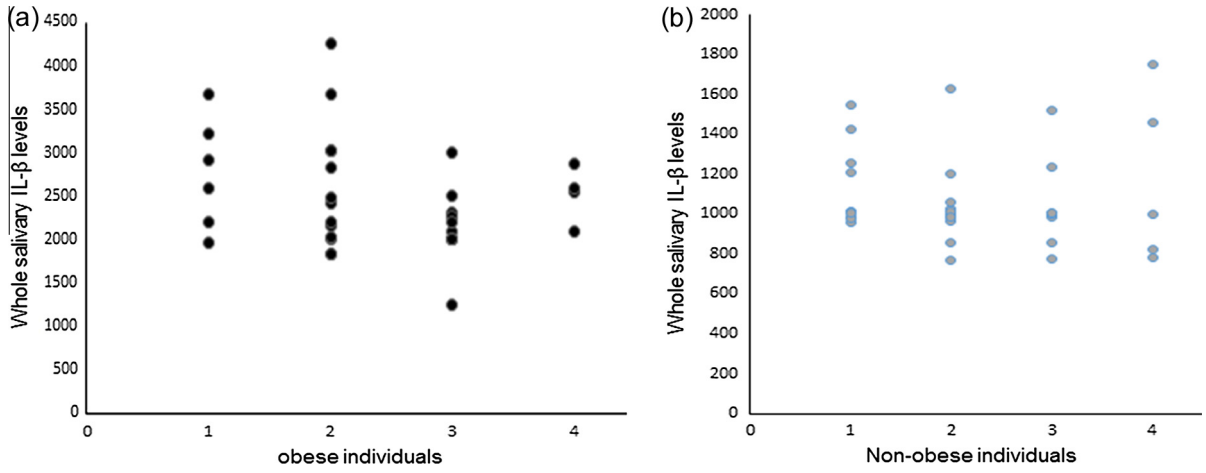

Fig. 2. Dot-plot demonstrating individual levels of IL-6 among obese and non-obese individuals.

apy reduce peri-implant soft tissue inflammation and whole salivary IL-6 and IL-1β in obese patients requires further investigation [34,35]. It is highly recommended that clinicians should educate obese patients seeking implant treatment regarding the association between obesity and peri-implant inflammation. In addition, obese patients with osseointegrated implants must follow strict oral hygiene regimen (due to increased susceptibility to inflammatory process) to prevent inflammation and maintain optimum dental and peri-implant tissue health [36].

5. Conclusion

Clinical and radiographic peri-implant inflammatory parameters were worse, and whole salivary IL-6 and IL-1β were higher in obese than non-obese subjects. Obese patients are at greater risk of peri-implant inflammation than non-obese healthy subjects.

Acknowledgements

The authors extend their sincere appreciations to Deanship of Scientific Research at King Saud University for its funding this prolific research group (PRG-1437-38).

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